PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

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in its capacity as elected Office

Date of mailing (day/month/year) 09 February 2000 (09.02.00)	
International application No. PCT/GB99/01777	**Applicant's or agent's file reference** 39763/JMD
International filing date (day/month/year) 04 June 1999 (04.06.99)	**Priority date** (day/month/year) 06 June 1998 (06.06.98)
Applicant PARSONS, Philip, James et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

06 January 2000 (06.01.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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09/700909 16

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
39763/JMD		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/01777	04/06/1999	06/06/1998
International Patent Classification (IPC) or national classification and IPC		
C07H17/00		
Applicant		
CENES LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06/01/2000	26.06.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Romano-Götsch, R Telephone No. +49 89 2399 8874

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/01777

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

2-18	as originally filed			
1	as received on	14/06/2000	with letter of	14/06/2000

Claims, No.:

1-7	as received on	08/03/2000	with letter of	23/02/2000
8-13	as received on	14/06/2000	with letter of	14/06/2000

Drawings, sheets:

1/2,2/2	as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-13
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-13
	No:	Claims	

2. Citations and explanations

see separate sheet

The following documents, cited in the ISR, are referred to:

D1: WO-A-93 03051 (cited in the application)
D2: Vlahov, J. et al., *Liebigs Ann. Chem.* (1983), (4), 570-4
D3: Kornilov, et al., *Russ. J. Biorg. Chem.*, **23(8)**, (1997), 655-666
D4: WO-A-96 28451
D5: Mignat, C., et al., *J. Pharm. Sci.*, **85(7)**, (1996), 690-694
D6: Wawrzynow,A., et al., *J.Chem.Thermodyn.*, 30(6),(1998), 713-722
D7: WO-A-93 05057 (cited in the application)
D8: Lacy,C.,et al., *Tetrahedron Letters*, **36 (22)**, (1995), 3949-3950
D9: Hidetoshi, Y. et al., *Chemical and Pharmaceutical Bulletin*, JP,TOKYO, **16(11)**, (1968), 2114-2119 (cited in the application)

V.

None of the document D1-D9 discloses the method for the preparation of Morphine-6-glucuronide (M6G) claimed in claims 1-7. Therefore, the subject-matter of claims 1-7 meets the requirements of Art. 33(2) PCT.

The compounds(10), (11), (12), (14), (15), (16) claimed in claims 8-13 are known from the prior art documents D1-D9. However, their use in the synthetic route on file as claimed in claims 8-13, which are purpose-limited product claims, is not disclosed nor suggested in said prior art. It follows that the claimed matter 8-13 meets the requirements of Art. 33(2) and (3) PCT.

Document D2-D5 does not relate to the synthesis of M6G. Thus, they are not considered relevant for the evaluation of inventive step for the claimed matter 1-7.

Documents D1, D7, D8, D9 are relevant prior art documents. In particular, D1 is regarded as the closest prior art.

According to D1 (p. 10) "This invention uses D-glucurono-6,3-lactone which is converted to esters of tetra-O-acyl-ß-D-glucopyranuronates (2) (where the acyl group could include...**pivalyl**,...). The product could then be condensed **directly** in the presence of a catalyst such as trimethylsilyl triflate or a Lewis acid, with morphine or a derivative whereby the phenolic OH group is protected, e.g. as a ... pivalyl ... After condensation, protecting groups can be removed by hydrolysis or other selective cleavage."

Differently from D1, in the process on file the methyl 1(ß),2,3,4-tetra-O-pivaloyl glucuronate is further reacted to obtain the methyl 1-α,2-ethylorthopivalate-3,4-di-O-pivaloylglucuronate, prior the condensation with the 3-O-pivaloylmorphine.

Since D1 does not suggest modifying the method therein disclosed in a way to render

obvious the process on file, the subject-matter of claims 1-7 is regarded as inventive over D1.

The synthesis of M6G according to D7-D9 does not proceed via the methyl 1(β),2,3,4-tetra-O-pivaloylglucuronate, rather via the methyl 1(β),2,3,4-tetra-O-acetyl glucuronate (D7, D9) or the methyl 1-deoxy-1-α-bromo,2,3,4-tri-O-acetyl glucuronate(D8). Thus, an inventive step for the claimed matter 1-7 over D7-D9 is acknowledged.

Morphine-6-Glucuronide Synthesis

The invention provides a novel method for synthesising Morphine-6-Glucuronide (M6G) and intermediates therefor.

Synthesis of M6G from 3-acetylmorphine and methyl 2-α-bromo-3,4,5-tri-O-acetylglucuronate is described by Lacy, C., *et al.* (*Tetrahedron Letters*, 36 (22), (1995), 3949-3950).

Hidetoshi, Y. *et al.*, (*Chemical and Pharmaceutical Bulletin*, JP, TOKYO, 16 (11), (1968), 2114-2119) describe synthesis of M6G by reaction of 3-acetyl-morphine with a bromo derivative of glucuronic acid to form a Methyl [3-acetylmorphin-6-yl-2,3,4-tri-O-acetyl-β-D-glucopyranosid] uronate intermediate which is subsequently hydrolysed to M6G.

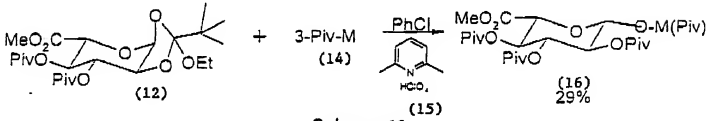
WO 93/05057 discloses preparation of M6G by reaction of 3-acetyl morphine with methyl 1α-bromo, 1-deoxy, 2,3,4-tri-O-acetyl D glucopyranuronate and subsequently hydrolysing the resulting intermediate to M6G.

In order to synthesise M6G the major problem to overcome is to obtain the glycoside linkage with very high β-selectivity since prior methods produce the α-anomer.

One method for obtaining high β-selectivity is to use trichloroimidate as the leaving group, as shown in WO 93/03051: Figure 1 (Salford Ultrafine Chemicals and Research Limited).

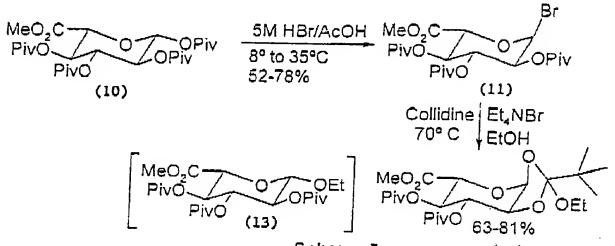
Claims

1. A method for the preferential synthesis of the β-anomer of M6G which includes the step shown in Scheme 10:



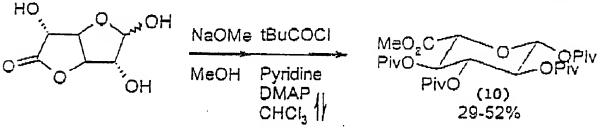
Scheme 10

2. Synthesis according to claim 1 which includes the step shown in Scheme 7:



Scheme 7

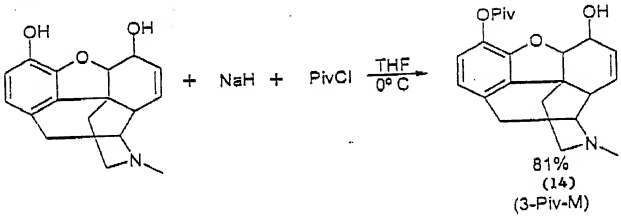
3. Synthesis according to claim 1 or 2 which includes the step shown in Scheme 6:



Scheme 6

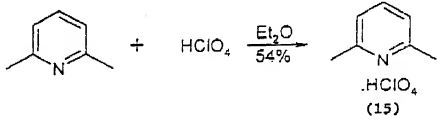
wherein use of DMAP is optional.

4. Synthesis according to any preceding claim which includes the step shown in scheme 8:



Scheme 8

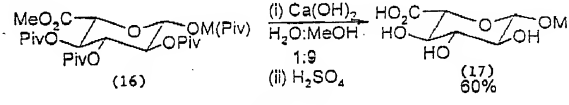
5. Synthesis according to any preceding claim which includes the step shown in Scheme 9:



Scheme 9

6. Synthesis according to any preceding claim which includes a step to hydrolyse the protecting groups from compound 16.

7. Synthesis according to claim 6 in which the hydrolysis is as shown in Scheme 11:



Scheme 11

8. A compound of formula (12) as defined in claim 2 or a derivative thereof for use in a method according to claim 1.

9. Use of a compound of formula (10) as defined in claim 1 or a derivative thereof in a method according to claim 2.

10. Use of a compound of formula (11) as defined in claim 2 or a derivative thereof in a method according to claim 2.

11. Use of a compound of formula (14) as defined in claim 3 or a derivative thereof in a method according to claim 1.

12. Use of a compound of formula (15) as defined in claim 4 or a derivative thereof in a method according to claim 1.

13. Use of a compound of formula (16) as defined in claim 5 or a derivative thereof in a method according to claim 7.

INTERNATIONAL SEARCH REPORT

National Application No
PCT/GB 99/01777

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07H17/00 C07H9/04 C07H13/04 C07D489/02 C07D213/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 03051 A (SALFORD ULTRAFINE CHEM & RES) 18 February 1993 (1993-02-18) cited in the application	1,8,10, 12,13
A	page 16 page 19, last paragraph claim 1	3,7
X	VLAHOV, JONTSCHO ET AL: "An improved synthesis of.beta.-glucosiduronic acid derivatives" LIEBIGS ANN. CHEM. (1983), (4), 570-4 , XP002123583 page 571, compounds 5 and 6	8,9

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
23 November 1999	03/12/1999

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages .	Relevant to claim No.
X	KORNILOV A. V. ET AL.: "Synthesis of oligosaccharides related to the HNK-1 antigen. 1. Synthesis of selectively protected allyl 3-O-'methyl (beta-D-glucopyranosyl)uronate!-beta-D-galactopyranoside" RUSS. J. BIOORG. CHEM., vol. 23, no. 8, 1997, pages 655-666, XP000856215	9
A	page 658, compound 21	2

X	WO 96 28451 A (EURO CELTIQUE SA ;MIGNAT CHRISTIAN (DE); HEBER DIETER (DE); ZIEGLE) 19 September 1996 (1996-09-19)	10,12
A	page 8 page 9, compound No 10 claims 1,3	3

X	MIGNAT, CHRISTIAN ET AL: "Synthesis, Opioid Receptor Affinity, and Enzymic Hydrolysis of Sterically Hindered Morphine 3-Esters" J. PHARM. SCI. (1996), 85(7), 690-694 , XP002123584	10,12
A	see table 1, compound 10 page 690, last paragraph -page 691, paragraph 1	3

X	WAWRZYNOW, ALICJA ET AL: "A comparison of acid-base properties of substituted pyridines and their N-oxides in propylene carbonate" J. CHEM. THERMODYN. (1998), 30(6), 713-722 , XP000856067 page 716	11,12

X	WO 93 05057 A (IREPA INST REGIONAL DE PROMOTI) 18 March 1993 (1993-03-18)	13
A	page 2, line 1 - line 14 page 6, line 23 - line 26 examples 5-8	7

X	LACY C ET AL: "A SYNTHESIS OF MORPHINE-6-GLUCURONIDE" TETRAHEDRON LETTERS, vol. 36, no. 22, 1995, page 3949-3950 XP000616116 ISSN: 0040-4039	13
A	page 3949 page 3950, compound 1.	7

	-/--	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HIDETOSHI YOSHIMURA ET AL: "METABOLISM OF DRUGS. LX.1). THE SYNTHESIS OF CODEINE AND MORPHINE GLUCURONIDES2)" CHEMICAL AND PHARMACEUTICAL BULLETIN,JP,TOKYO, vol. 16, no. 11, 1968, page 2114-2119 XP000614807 ISSN: 0009-2363	13
A	page 2115, chart 1 page 2116, line 3 - line 6 page 2119, paragraph 4	7

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9303051 A	18-02-1993	AT 173269 T	15-11-1998
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		AU 2389492 A	02-03-1993
		CA 2114838 A	18-02-1993
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		EP 0597915 A	25-05-1994
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		GR 3029369 T	28-05-1999
		HU 68169 A	29-05-1995
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		NO 940349 A	16-03-1994
		US 5621087 A	15-04-1997
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		AU 5108596 A	02-10-1996
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		AU 2555592 A	05-04-1993
		EP 0602151 A	22-06-1994

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(30) Priority Data:

9812097.5	6 June 1998 (06.06.98)	GB
9900833.6	15 January 1999 (15.01.99)	GB

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(72) Inventors; and

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(74) Agent: DAVIES, Jonathan, Mark; Reddie & Grose, 16 Theobalds Road, London WCLX 8PL (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

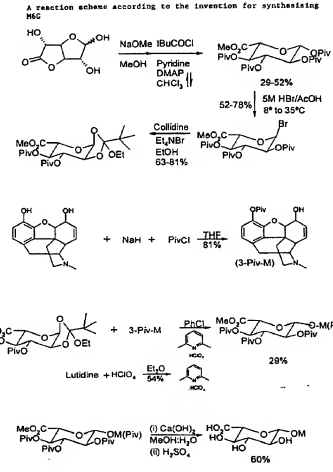
Without international search report and to be republished upon receipt of that report.

(54) Title: MORPHINE-6-GLUCURONIDE SYNTHESIS

(57) Abstract

The invention provides a novel method for synthesising M6G, and intermediates therefor. In order to synthesise M6G the major problem to overcome is to obtain the glycoside linkage with very high β-selectivity since prior methods produce the α-anomer. The invention provides a method for the preferential synthesis of the β-anomer of M6G which includes the step shown in Scheme 6: wherein use of DMAP is optional.

A reaction scheme according to the invention for synthesising M6G



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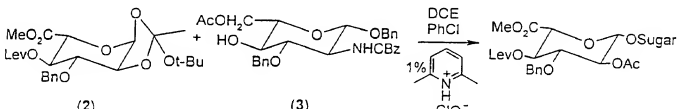
Morphine-6-Glucuronide Synthesis

The invention provides a novel method for synthesising M6G, and intermediates therefor.

In order to synthesise M6G the major problem to overcome is to obtain the glycoside linkage with very high β-selectivity since prior methods produce the α-anomer.

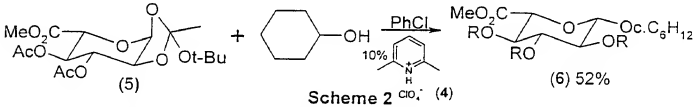
One method for obtaining high β-selectivity is to use trichloroimidate as the leaving group, as shown in WO 93/03051: Figure 1 (Salford Ultrafine Chemicals and Research Limited).

Orthoesters are simple to synthesise from their respective bromides[1]. There is a reaction reported in the literature[2] between the glucuronate orthoester (2) and the sugar derivative (3) catalysed by lutidinium perchlorate[3] (4) (Scheme 1).



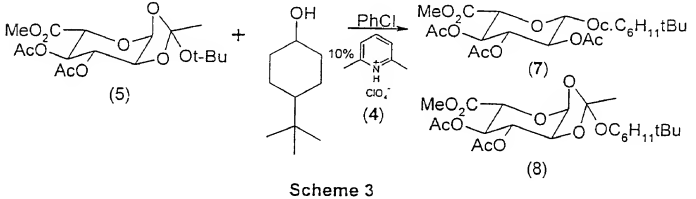
Scheme 1

When this reaction was repeated with the t-butyl orthoacetate (5) and cyclohexanol (6 equivalents), the desired product (6) was isolated in 9% yield. Two other products also suggested that they were the desired product, but with the loss of one acetyl group, isolated in a combined yield of 43% (Scheme 2).



Scheme 2

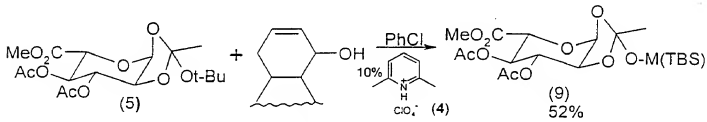
When 1.2 equivalents of 4-*tert*-butylcyclohexanol was used, the desired compound (7) was obtained in 17% yield. Other compounds obtained from the reaction also appeared to contain the desired peaks in the nmr, but after further examination proved to be the product of transorthoesterification (8) (Scheme 3).



Scheme 3

Reaction of orthoester (5) with protected morphine

Initially, 1.2 equivalents of 3-TBS protected morphine and the orthoester (**5**) were dissolved in chlorobenzene and half of the solvent was distilled off before 0.1 equivalents of lutidinium perchlorate (**4**) in chlorobenzene was added. The solvent was continuously distilled off while fresh solvent was added, and after 2.5 h another compound was formed with similar tlc properties to the protected morphine. Workup and chromatography gave a compound which corresponded to trans-orthoesterified material (**9**). None of the desired material was obtained (Scheme 4).



Scheme 4

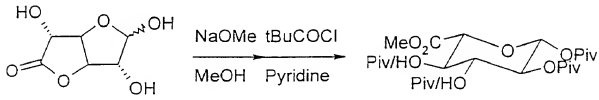
This product (**9**) was resubmitted to the reaction conditions (0.1 equivalents of lutidinium perchlorate and protected morphine in refluxing chlorobenzene) with no new products formed after 4h. Two further reactions were attempted using two equivalents of orthoester (**5**) and 0.2 equivalents of lutidinium perchlorate and 1 equivalent of orthoester (**5**) and 1.2 equivalents of lutidinium perchlorate, but both gave varying yields of orthoester (**9**).

We have concluded that a different, more bulky, alkyl group was needed on the orthoester to hinder attack there. Initially, the isopropyl group was examined. However, the initial reaction, perisobutyrylation, failed to give a compound which recrystallised from petrol, so the α and β anomers could not be separated. Therefore, attention focussed on the pivaloyl group.

The invention is further described with reference to the accompanying figure 2 which shows a summary of a reaction scheme according to the invention for synthesising M6G.

Synthesis of the Perpivalated Glucuronide

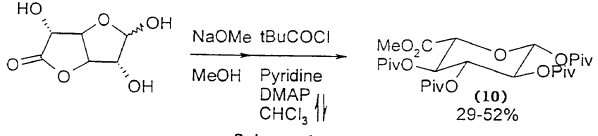
Synthesis of perpivalated glucuronide proved troublesome at first, giving a mixture of 3 and 4 non-pivalated material (scheme 5).



Scheme 5

A search through the literature revealed that glucose can be perpivalated by heating the reaction to reflux for 3h. and then stirring it for 7 days.

When this reaction was repeated on ring-opened glucurono-3,6-lactone (Scheme 6), perpivalated product **(10)** was obtained by crystallisation of the crude product from MeOH (or EtOH) and water and drying the crystals by dissolving them in DCM, separating any water present, drying, and then evaporating the organic layer to give the product in 29-52% yield, a substantial improvement on previous yields for this step.



Scheme 6

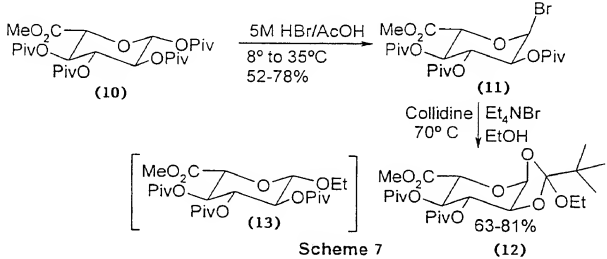
DMAP was added to aid perpivalation, although there has been no evidence to suggest that this is necessary. The variation in the yields quoted is probably due to the amount of MeOH left over from the first step. The high yield quoted (52%) was obtained by using 6 (instead of 5) equivalents of tBuCOCl. A slight

colouration of the final product proved no handicap in the next step, as after a silica plug and recrystallisation, pure white crystals were obtained.

Synthesis of the Orthoester (6)

Conversion of the perpivalated material **(10)** to the α-bromide **(11)** required gentle heating (to approxiamately 35° C) to dissolve the substrate in the reaction mixture. The reaction proceeded very cleanly by tlc analysis, showing a spot to spot conversion. Attempts to reduce the amount of HBr used to five equivalents led to incomplete conversion of the starting material, so 12 equivalents were used as before. The product was slowly crystallised from EtOH/water or MeOH/water to give long white crystals in a yield of 52-78%. High yields were always obtained when fresh HBr/AcOH was used. The crystals were dried by again dissolving them in dichloromethane, the water separated, and the organic layer dried and evaporated.

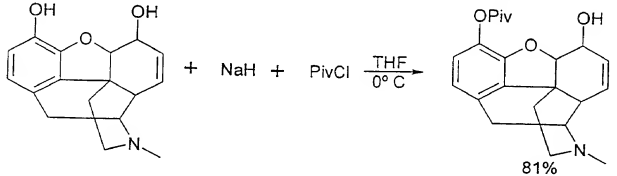
The orthoester **(12)** was obtained in 63-81% yield by stirring a 1:1 mixture of EtOH:collidine at 70° C (oil bath temperature) with the bromide **(11)** and 0.8 equivalents of Et_4NBr (Scheme 7). The product can easily be crystallised from EtOH/water water or MeOH/water as white crystals, with a trace of collidine still present (detected by smell!) but which doesn't effect the next reaction. An interesting by-product from this reaction (obtained in about 10%) is the result of EtOH attacking the anomeric position to give the β-anomer **(13)** Again, the difficulty in drying the crystals meant that they were dissolved in petrol (40-60), the water separated, and the organic layer dried and evaporated.



Scheme 7

Synthesis of 3-Pivalated morphine (14)

Selective deprotonation of the phenolic OH of morphine was achieved using NaH (surprisingly, the anion turns out to be soluble in THF) and trimethylacetyl chloride was added dropwise to give the desired product after recrystallisation from MeOH/water (Scheme 8). Again, the difficulty in drying the crystals meant that they were dissolved in dichloromethane, the water separated, and the organic layer dried and evaporated to give a white powder in 81% yield.

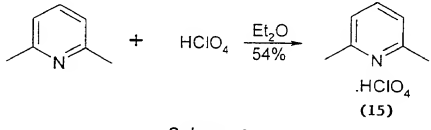


Scheme 8

1.1 equivalents of trimethylacetyl chloride were used, but this led to some dipivalated morphine which proved difficult to recrystallise apart from mono-pivalated morphine **(14)** or the protected M6G **(16)**. Thus, it would be advantagous in the future to use 1 equivalent of trimethylacetyl chloride.

Synthesis of Lutidinium Perchlorate (15)

This was achieved by simply adding aqueous perchloric acid to an ether solution of lutidine (excess, as this remains in the Et_2O layer) (Scheme **9**) and evaporating the water until crystals form, which were collected by filtration.



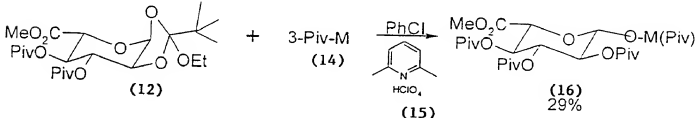
Scheme 9

The crystals are deliquescent and thus need to be dried under high vacuum prior to use.

Other acid catalysts have been investigated in the coupling reaction below, but with no success. However, this compound has shown no tendencies to decompose, proving both thermal and shock stable, so shouldn't prove a problem on scale up.

Coupling of the orthoester (12) with 3-pivalated morphine (14)

Coupling the orthoester **(12)** to 1.1 equivalents of 3-pivalated morphine **(14)** was achieved by adding 0.1 equivalents of lutidinium perchlorate **(15)** every 15 min. until 1.2 equivalents had been added to the distilling chlorobenzene. The reaction was then stirred under reflux for a further 2h. to give a mixture of 3-pivalated morphine **(14)** protected M6G **(16)** and much less polar materials. Work-up and crude purification by chromatography gave protected M6G **(16)** and 3-pivalated morphine **(14)** which was purified by recrystallisation from MeOH/(water, small quantity) to give **(16)** in 29% yield (with no detectable quantity of α-anomer or trans-orthoesterified material from nmr analysis) (Scheme **10**).



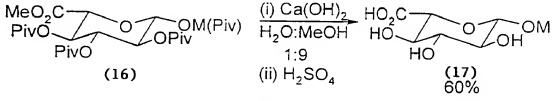
Scheme 10

This yield is the greatest amount obtained from this reaction and further improvements might be possible. Lutidinium perchlorate **(15)** was added every 15 min. as a solid appeared to crystallise from the reaction mixture (presumably the 3-pivalated morphine perchlorate) and, if no more catalyst is added, the major product turned out to be the trans-orthoesterified material (similar to orthoester **(9)** in Scheme **14**). If 1.2 equivalents of lutidinium perchlorate **(15)** was added directly to the reaction, only 6% of coupled material was obtained (presumably as all the 3-pivalated morphine had been removed from the reaction as the

perchlorate salt). The main problem with adding the catalyst, is its insolubility in chlorobenzene lower than approxiamately 100° C. If it is possible on a large scale to add lutidinium perchlorate (15) in chlorobenzene at 100° C, this may prove not only simpler to add the catalyst, but also lead to increasing yields. The reaction also needs to be refluxed for an additional 2 hours after all the lutidinium perchlorate (15) has been added, to cause the trans-orthoesterified material to rearrange to the desired material.

Global Deprotection of Protected M6G (16)

Heating protected M6G (16) in MeOH until it dissolves before adding the water (which causes it to crystallise from the reaction mixture) and $Ca(OH)_2$ seems to be the mildest way of performing this reaction. After stirring for 3 days, the reaction gave, by tlc analysis, M6G (17) and morphine (Scheme 11).



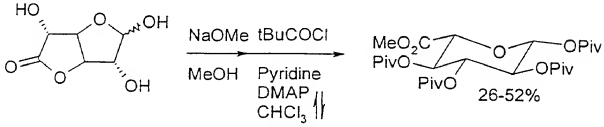
Scheme 11

The reaction was quite slow due to the insolubility of $Ca(OH)_2$ in water, but when the reaction is deemed to have finished by tlc analysis, 6.5 equivalents of sulfuric acid were added or until the reaction reached pH 4. The $CaSO_4$ so formed was filtered off and the trimethylacetic acid also formed was removed by washing the filtrate with DCM. Evaporating the water proved the hardest part of this reaction due to excessive foaming. Some $CaSO_4$ remains in the filtrate and this was removed by adding MeOH to crystallise it out. The residue produced after all the water had been evaporated was purified by repeated washing with MeOH as M6G is virtually insoluble in MeOH while morphine is soluble in it. The morphine present in the crude residue probably arrived there due to the di-pivalated morphine passing through the coupling reaction and then being deprotected to morphine in this final step. Hopefully, by using strictly 1 equivalent of trimethylacetyl chloride, this should eliminate the di-pivalated morphine, thus make purification of M6G even simpler, and increasing the yield for the final step.

The invention is further described in detail below by way of example only.

Example 1

Methyl 1β,2,3,4-tetra-*O*-pivaloylglucuronate



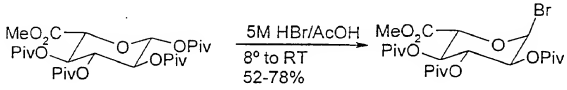
Glucurono-6,3-lactone (147 g, 0.8 mol) was stirred as a suspension in methanol (1L, not dried) under nitrogen. A catalytic amount of sodium methoxide (147 mg, 2.6 mmol) was added to the suspension, and after 2 hours most of the suspension was still present. The reaction proceeded very slowly at room temperature, ~18°C, but noticeably increased in rate when the reaction was warmed, therefore, the reaction was gently warmed to ~25°C. After another hour of stirring, most of the suspension had dissolved to leave a clear yellow solution that was then evaporated. The residue was found to be a solid, which tended to foam under vacuum, which made total removal of all the methanol difficult.

Chloroform (400mL), followed by 6 equivalents of pyridine (400mL, 4.8mol) and a catalytic amount of *N,N*-dimethyl-4-aminopyridine (4 g) was then added to the residue that slowly dissolved in this mixture. The solution was stirred using a magnetic stirrer plate and flea, but the problems encountered in continuously stirring this reaction would make an overhead mechanical stirrer preferable at this stage. The reaction was then cooled to 0°C and 5 equivalents of trimethylacetyl chloride (500mL, 4 mol) was added gradually, not allowing the reaction to warm to a temperature above ~8°C. The yellow/orange solution became colourless on addition of the first portion of trimethylacetyl chloride, and after approximately half of the volume was added, a white precipitate was observed (pyr.HCl). After addition was complete, the reaction was stirred overnight at room temperature before being heated at reflux for 2 hours, during

which time the reaction turned black with the white precipitate still present. Tlc analysis showed that the desired product had been produced (Rf 0.5, 1:1 Et_2O:petrol), but some mono-unprotected material remained (Rf 0.3 and 2.8, 1:1 Et_2O:petrol). The reaction was then allowed to cool to room temperature over 3 hours, then further cooled to 0°C before methanol was added gradually (this quenches the excess trimethylacetyl chloride to give methyl trimethylacetate, which is evaporated off with the solvent). The black solution was then poured into a 2L separating funnel, and washed with water (600 mL), 1M HCl (2 * 600 mL), water (600 mL), and saturated aqueous $NaHCO_3$ (2 * 600 mL). The organic layer was then dried with $MgSO_4$ and passed through approximately 5cm of silica on a sinter funnel (which removed a black baseline compound). The silica was washed with dichloromethane (100 mL) and the combined filtrates evaporated to leave a black viscous oil, which was re-dissolved in ethanol (~1L) and had water added until the solution turned turbid (~500mL). More ethanol was added until the turbid solution cleared, and the solution was left to crystallise overnight. The yellow crystals were dissolved in dichloromethane (300 mL) and any excess water removed by separation, the dichloromethane layer was then dried and evaporated.

The white powder (113.5 g, 26%) was then used in the next reaction.

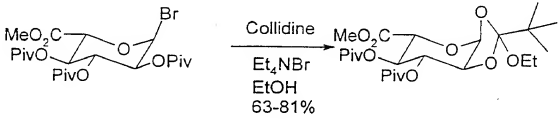
Methyl 1-deoxy-1-α-bromo,2,3,4-tri-*O*-pivaloylglucuronate



Methyl 1(β),2,3,4-tetra-*O*-pivaloylglucuronate (108.5 g, 0.2 mol) was dissolved in glacial acetic acid (500 mL) (with the aid of some gentle heating) and placed in a bath of cold water. 12 equivalents of 33% HBr in acetic acid (500 mL, 2.9 mol) were then added at a rate required to prevent the acetic acid freezing without the reaction exotherming too greatly. After the addition was complete, the reaction was allowed to warm to room temperature. If any white solid (starting material) persisted, gentle warming was applied to the reaction until it dissolved and the reaction then allowed to cool and stir overnight. The orange/brown solution was then cautiously poured into dichloromethane (500 mL) / water (500 mL), the organic layer separated, washed with water (500 mL) and saturated $NaHCO_3$ (500 mL) (with care to avoid too rapid an evolution of CO_2). The organic layer was then dried ($MgSO_4$) and passed through approximately 2 cm of silica, the silica was washed with more dichloromethane (50 mL) and the combined filtrates evaporated (taking care to remove all the dichloromethane). The residue was then dissolved in EtOH (~400 mL) and water added until the reaction turned turbid. More ethanol was added until the solution just turned clear and the product allowed to crystallise overnight which were collected by filtration. The crystals were dissolved in dichloromethane and the organic layer separated from any water that remained, dried ($MgSO_4$), and evaporated.

The white powder (76 g, 72%) was then used in the next reaction.

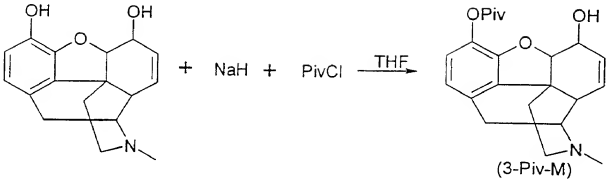
Methyl 1α,2-ethylorthopivalate-3,4-di-*O*-pivaloylglucuronate



Methyl 1-deoxy-1-α-bromo,2,3,4-tri-*O*-pivaloylglucuronate (69 g, 0.13 mol) was dissolved in collidine (300 mL) (pre-dried by distilling onto activated 3Å sieves) and ethanol (300 mL) (pre-dried by distilling from NaOEt onto activated 3Å sieves). 0.8 equivalents of pre-dried tetraethylammonium bromide (22 g, 0.1 mol) was then added to the reaction, which was stirred at 60°C (oil-bath temperature 70°C) overnight. The reaction was then cooled and poured into dichloromethane (500 mL) / water (500 mL) and the organic layer separated, dried ($MgSO_4$), and evaporated. The collidine was removed by low-pressure distillation (total evaporation is not necessary), the residue dissolved in EtOH (~400mL), and water added until the product started to crystallise out. The white crystals were collected by filtration and dissolved in petrol. The organic layer was then separated from any water that remained, dried ($MgSO_4$), and evaporated.

The white powder (50g, 78%) was then used in the next reaction.

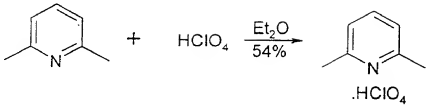
3'-*O*-Pivaloylmorphine



Morphine (12g, 42 mmol) was added portionwise to a THF (80 mL, Na dried) suspension of 1.05 equivalents of petrol washed NaH (60 % dispersion in oil, 1.768 g, 44 mmol) at 0° C. After stirring for 1h at room temperature, 1.1 equivalents of trimethylacetyl chloride (5.7 mL, 46 mmol) were added to the clear reaction mixture at 0° C and eventually a white solid precipitated from the reaction. After 1h., MeOH (10 mL) followed by saturated aqueous sodium bicarbonate (100 mL) were added to the reaction which was then extracted with Et_2O (2x200 mL). The combined extracts were washed with brine (200 mL), dried, and evaporated. The residue was recrystallised from MeOH/water and the crystals dissolved in dichloromethane and the organic layer separated from any water that remained, dried ($MgSO_4$), and evaporated.

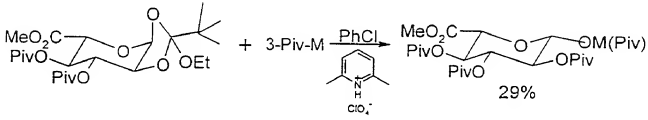
The white powder (12.6 g, 81%) was then used in the next reaction.

Lutidinium Perchlorate



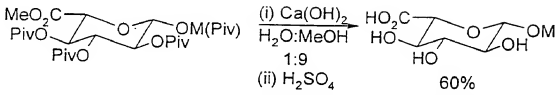
A 60% aqueous solution of perchloric acid (29 mL, 0.27 mol) was added to 1.1 equivalents of lutidine (34 mL, 0.29 mL) in Et_2O (250 mL) at 0° C. After stirring for 0.5h. at room temperature, the aqueous layer was separated and the water evaporated until a white solid crystallised from the water, the crystals filtered off and washed with Et_2O to give the product as a white crystalline solid (30 g, 54%). The product was dried under high vacuum prior to use.

Methyl 1β-6'-*O*-(3'-*O*-pivaloylmorphine)-2,3,4-tri-*O*-pivaloylglucuronate



A chlorobenzene (400 mL) (distilled from CaH_2 onto activated 3Å sieves) solution of 1.1 equivalents of 3-*O*-pivaloyoloxymorphine (8.49 g, 23 mmol) and methyl 1α,2-ethylorthopivalate-3,4-di-*O*-pivaloylglucuronate (10 g, 20 mmol) was heated to reflux to distil off approximately half of the solvent. 0.1 Equivalents of lutidinium perchlorate (415 mg, 2 mmol) was then added to the reaction that was still at reflux. The reaction was then stirred at reflux for 15 min with chlorobenzene continuously distilled off and fresh chlorobenzene added. After this time, a further 0.1 equivalents of lutidinium perchlorate (415 mg, 2 mmol) was then added to the reaction. This procedure was repeated every 15 min until 1.2 equivalents of lutidinium perchlorate (5.2 g, 25 mmol) had been added. The reaction was then stirred at reflux for 2 hours with chlorobenzene continuously distilled off and fresh chlorobenzene added. After this time, the reaction was allowed to cool and then poured into dichloromethane (500 mL) / water (500 mL), the organic layer separated, washed with saturated aqueous sodium bicarbonate (500 mL), dried, and evaporated. The residue, after some of the chlorobenzene had been removed under low pressure, was applied to the top of a silica column and eluted with diethyl ether to remove the non-polar by-products and then with 5% methanol in dichloromethane. The desired product was separated from 3-Piv-M by recrystallisation from MeOH/water to give a white crystalline powder (4.76 g, 29%).

Morphine-6-gluconoride



Methyl 1β-6'-*O*-(3'-*O*-pivalayloxymorphine)-2,3,4-tri-*O*-pivaloylglucuronate (3.06 g, 3.77 mmol) was dissolved in MeOH (60 mL) (with the help of some heating) and had water (7 mL) followed by 6.5 equivalents of calcium hydroxide (1.817 g, 24.5 mmol) added to it. The reaction was stirred for two days when water (60 mL) was added and the reaction stirred for a further day until the reaction was shown to be complete by tlc analysis (Rf 0.3, 45% nBuOH; 15% water; 20% acetone; 10% acetic acid; 10% of a 5% aqueous solution of ammonia). 6.5 equivalents of 0.25M aqueous sulphuric acid (98 mL, 24.5 mmol) were added (pH 4) and the reaction stirred for 1 hour. The reaction was then filtered to remove $CaSO_4$ and the solid washed with water (30 mL). The filtrate was then washed with DCM (2x100 mL), three quarters of the water evaporated and the same quantity of MeOH added. The white solid (mainly $CaSO_4$) was then filtered and the filtrate evaporated. The residue (1.56 g) had MeOH (100 mL) added and the white solid filtered and repeatedly washed with MeOH to give the desired compound (1.05 g, 60%) which could, according to the literature, be recrystallised from H_2O/MeOH (although this has not been performed on this material).

References

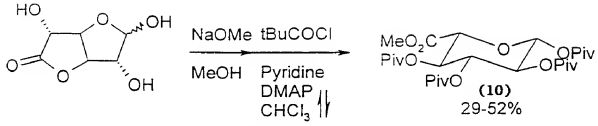
1. For a review of orthoesters and their synthetic applications see N. K. Kochetkov and A. F. Bochkov, *Recent Developments in the Chemistry of Natural Carbon Compounds*, Ed. R. Bognár, V. Bruckner, and Cs. Szántay, Akadémiai Kiadó: Budapest, 1971, vol. 4, p.77-191.

2. H. P. Wessel, L. Labler, and T. B. Tschopp, *Helv. Chim. Acta.*, 1989, **72**, 1268.

3. The use of 2,6-dimethylpyridinium perchlorate (**4**) was first reported by N. K. Kochetkov, A. F. Bochkov, T. A. Sokolovskaya, and V. J. Snyatkova, *Carbohydr. Res.*, 1971, **16**, 17.

Claims

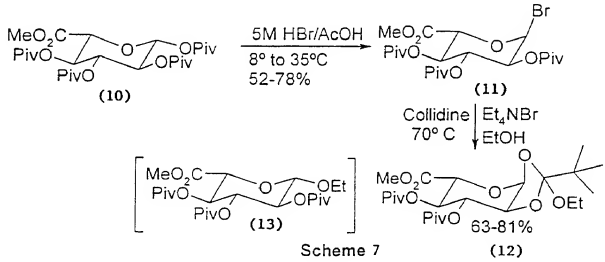
1. A method for the preferential synthesis of the β-anomer of M6G which includes the step shown in Scheme 6:



Scheme 6

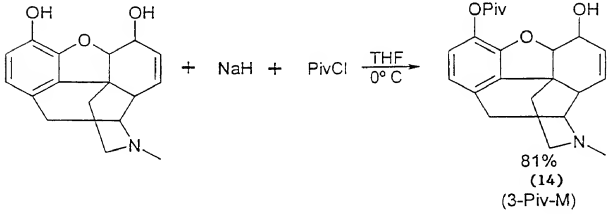
wherein use of DMAP is optional.

2. Synthesis according to claim 1 which includes the step shown in Scheme 7:



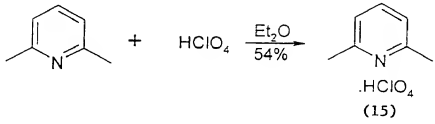
Scheme 7

3. Synthesis according to claim 1 or 2 which includes the step shown in scheme 8:



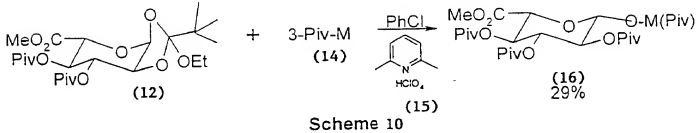
Scheme 8

4. Synthesis according to any preceding claim which includes the step shown in Scheme 9:



Scheme 9

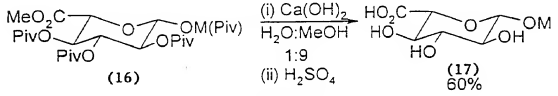
5. Synthesis according to any preceding claim which includes the step shown in Scheme 10:



Scheme 10

6. Synthesis according to claim 5 which includes a step to hydrolyse the protecting groups from compound 16.

7. Synthesis according to claim 6 in which the hydrolysis is as shown in Scheme 11:



Scheme 11

8. A compound of formula (10) or derivative thereof for use in a method according to claim 1.

9. A compound of formula (11) or (12) or a derivative thereof for use in a method according to claim 2.

10. A compound of formula (14) or a derivative thereof for use in a method according to claim 3.

11. A compound of formula (15) or a derivative thereof for use in a method according to claim 4.

12. A compound of formula (12), (14), (15) or (16) or a derivative thereof for use in a method according to claim 5.

13. A compound of formula (16) or (17) or a derivative thereof for use in a method according to claim 7.

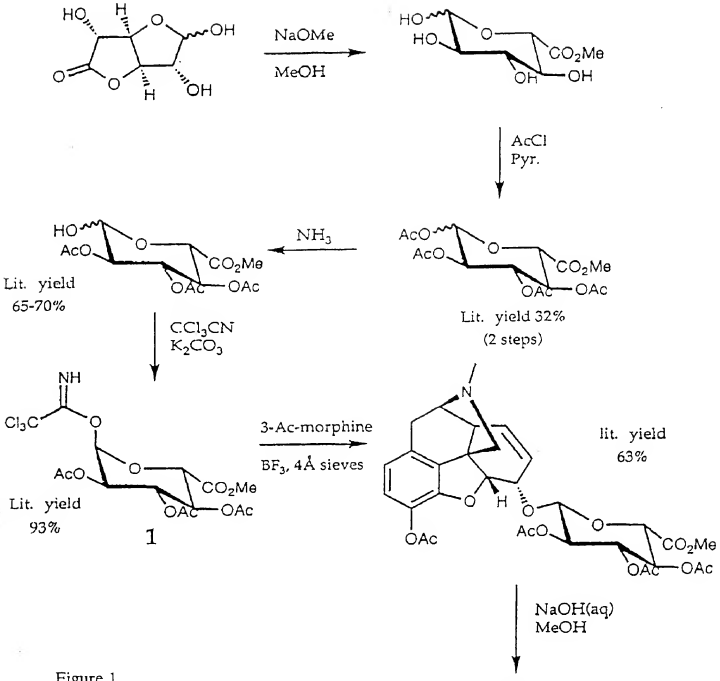
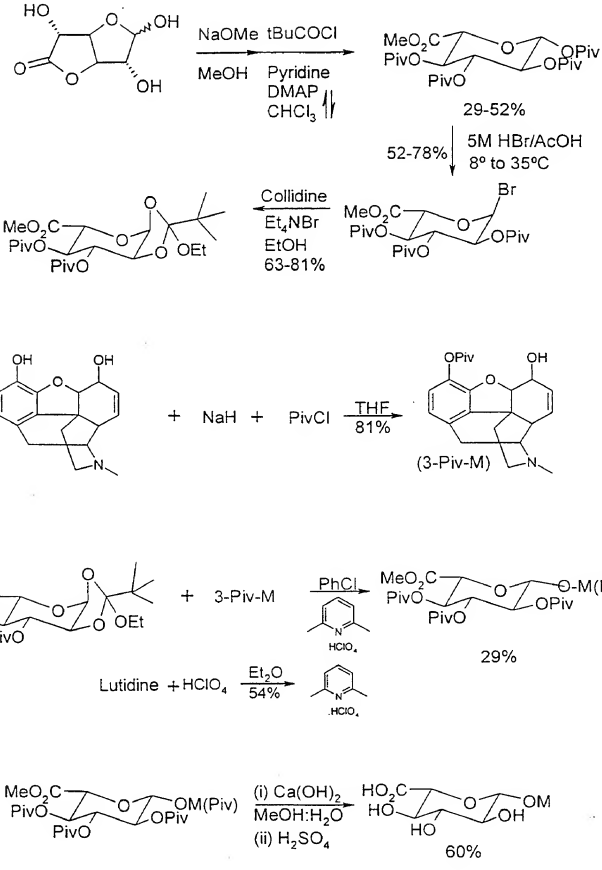


Figure 1

Prior Art

Figure 2

A reaction scheme according to the invention for synthesising M6G



PATENT COOPERATION TREATY

PCT

09/700909

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
39763/JMD		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 99/01777	04/06/1999	06/06/1998
Applicant		
CENES LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

[X] as suggested by the applicant.

[ ] None of the figures.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/01777

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07H17/00 C07H9/04 C07H13/04 C07D489/02 C07D213/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 03051 A (SALFORD ULTRAFINE CHEM & RES) 18 February 1993 (1993-02-18) cited in the application	1,8,10, 12,13
A	page 16 page 19, last paragraph claim 1 ---	3,7
X	VLAHOV, JONTSCHO ET AL: "An improved synthesis of.beta.-glucosiduronic acid derivatives" LIEBIGS ANN. CHEM. (1983), (4), 570-4 , XP002123583 page 571, compounds 5 and 6 ---	8,9

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 November 1999	03/12/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Held, P

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	KORNILOV A. V. ET AL.: "Synthesis of oligosaccharides related to the HNK-1 antigen. 1. Synthesis of selectively protected allyl 3-O-'methyl (beta-D-glucopyranosyl)uronate!-beta-D-gal actopyranoside" RUSS. J. BIOORG. CHEM., vol. 23, no. 8, 1997, pages 655-666, XP000856215	9
A	page 658, compound 21	2

X	WO 96 28451 A (EURO CELTIQUE SA ;MIGNAT CHRISTIAN (DE); HEBER DIETER (DE); ZIEGLE) 19 September 1996 (1996-09-19)	10,12
A	page 8 page 9, compound No 10 claims 1,3	3

X	MIGNAT, CHRISTIAN ET AL: "Synthesis, Opioid Receptor Affinity, and Enzymic Hydrolysis of Sterically Hindered Morphine 3-Esters" J. PHARM. SCI. (1996), 85(7), 690-694 , XP002123584	10,12
A	see table 1, compound 10 page 690, last paragraph -page 691, paragraph 1	3

X	WAWRZYNOW, ALICJA ET AL: "A comparison of acid-base properties of substituted pyridines and their N-oxides in propylene carbonate" J. CHEM. THERMODYN. (1998), 30(6), 713-722 , XP000856067 page 716	11,12

X	WO 93 05057 A (IREPA INST REGIONAL DE PROMOTI) 18 March 1993 (1993-03-18)	13
A	page 2, line 1 - line 14 page 6, line 23 - line 26 examples 5-8	7

X	LACY C ET AL: "A SYNTHESIS OF MORPHINE-6-GLUCURONIDE" TETRAHEDRON LETTERS, vol. 36, no. 22, 1995, page 3949-3950 XP000616116 ISSN: 0040-4039	13
A	page 3949 page 3950, compound 1.	7

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HIDETOSHI YOSHIMURA ET AL: "METABOLISM OF DRUGS. LX.1). THE SYNTHESIS OF CODEINE AND MORPHINE GLUCURONIDES2)" CHEMICAL AND PHARMACEUTICAL BULLETIN,JP,TOKYO, vol. 16, no. 11, 1968, page 2114-2119 XP000614807 ISSN: 0009-2363	13
A	page 2115, chart 1 page 2116, line 3 - line 6 page 2119, paragraph 4	7

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 99/01777

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